Implications of Childhood Acute Lymphocytic Leukemia Studies for Children's Health Risk Assessment

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Abstract

Children are a susceptible subpopulation, and child-specific risk assessment approaches are critical in protecting children's health against exposure to environmental toxicants. To understand the biological basis of disease processes and potential role of environmental chemical exposures, both of which are critical for children's health risk assessment, studies on childhood disease are evaluated. Specifically, this evaluation focuses on acute lymphocytic leukemia (ALL), the most common form of childhood cancer representing ~25% of all cancer cases of children younger than 15 years in the U.S. A multi-stage model involving a prenatal initiating event and postnatal second event has been hypothesized to be involved in the induction of childhood ALL in most cases. This hypothesis is supported by the detection of ALL-associated chromosomal translocations/fusion genes both at birth and at ALL diagnosis; this detection indicates prenatal ALL initiation and recognizes preconceptional and prenatal periods as potentially critical windows of exposure. Risk factors reported to be associated with childhood ALL are analyzed based on their linkage to the three potentially critical exposure windows: preconceptional, prenatal, and postnatal. Additionally, use of childhood ALL-associated fusion genes and gene polymorphisms, together or separately, as indicators of susceptibility is explored.

Table 1. Percent distribution of leukemia cases by type[a]: children vs. adults

Leukemia type	% Total leukemia cases	
	Children	Adults
Acute lymphocytic leukemia (ALL)	**78**	**11**
Acute myeloid leukemia (AML)	16	36
Chronic lymphocytic leukemia (CLL)	<1	24
Chronic myeloid leukemia (CML)	2	14

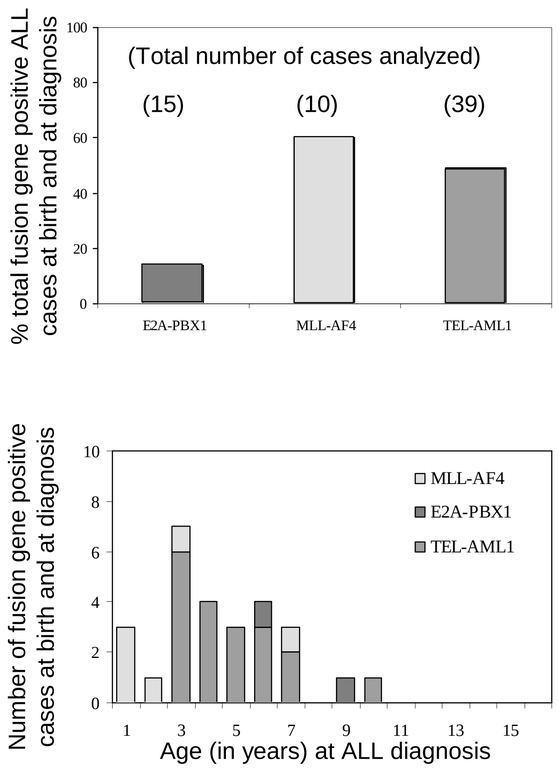
[a]U.S. data from http://www.cancer.org

Table 2. Percent distribution of chromosomal translocations in childhood ALL[a]

Chromosomal translocation(s)	Fusion gene(s)	% total ALL cases
t(1;19)	E2A-PBX1	5
t(4;11), t (9;11), t(11;19)	MLL fusions	6
t(9;22)	BCR-ABL	3-5
t(12;21)	**TEL-AML1**	**20-25**
Random		~30
None		30

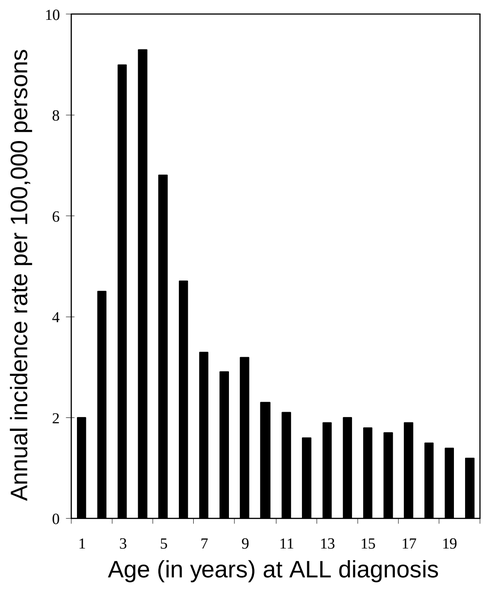
[a]References available upon request

Figure 1. Prenatal (in utero) initiation of childhood ALL: analysis of fusion genes at birth and at ALL diagnosis in single-born children[a]



[a]Based on seven published journal articles; references available upon request

Figure 2. Age-specific incidence rates of childhood ALL[a]



[a]U.S. data from http://www.cancer.org

Figure 3. Potential relationship among childhood ALL-causing events (multi-stage model), critical exposure windows, and exposure-dependent risk factors

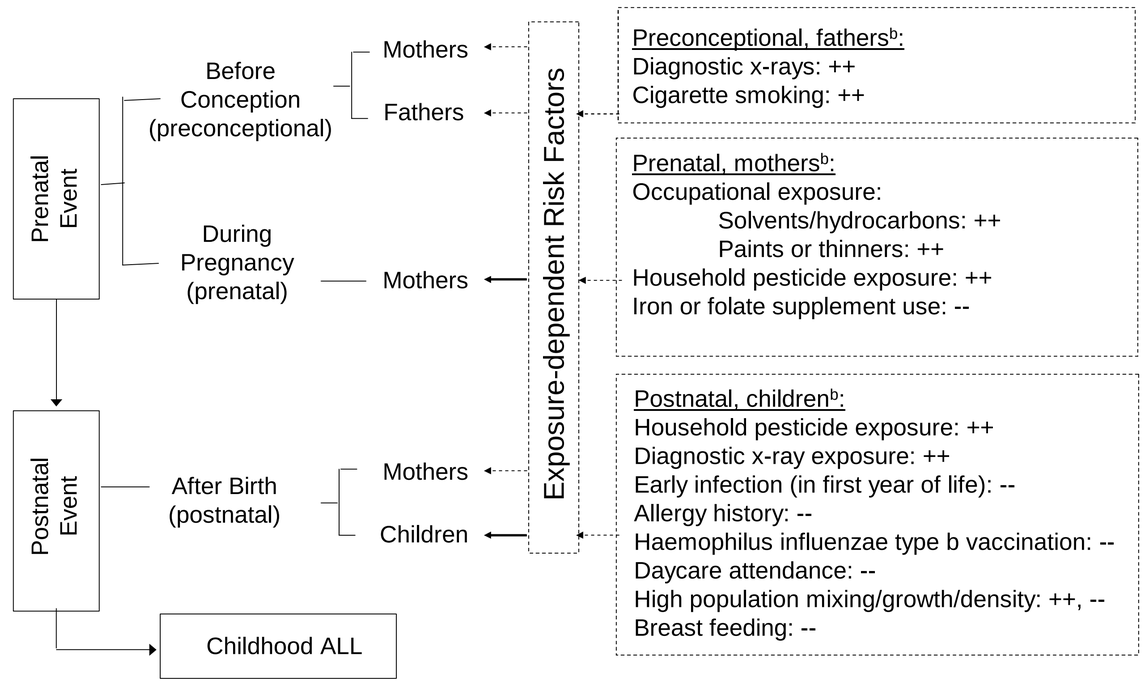


Table 3. Exposure-independent risk factors associated with childhood ALL[a]

Risk factor	Risk[b]
Maternal age (e.g., <20 years; >35 years)	++
Paternal age (e.g., >40 years)	++
Maternal reproductive history (e.g., miscarriage & fetal loss)	++
High birth order (e.g., fourth born)	++, --
High birth weight (e.g., >3800 g)	++
Family history of disease, cancer	++
Genetic/familial diseases (e.g., Down syndrome)	++
Gender, male	++
Race	++, --

Table 4. Genetic polymorphisms associated with childhood ALL[a]

Genetic polymorphism	Risk[b]
Cytochrome P-450 (CYP):1A1*2A (T6235C)	++
1A1m2 (A4889G); 2E1*5 (G1259C)	+
Glutathione S-transferase (GST): M1 (null genotype)	++
P1*B (A1578G)	+
N-acetyltransferase (NAT):	
1*4 (no mutation); 2*5C (T341C & A803G); 2*7B(C282T & G857A)	+
2*4 (no mutation)	-
Methylenetetrahydrofolate reductase (MTHFR): (C677T); (A1298C)	-
Quinone oxidoreductase (NQO): 1*2C (C609T); 1*3 (C465T)	+
Human leucocyte antigen (HLA)	
DPB1*0101; DQA1*05	-
DPB1*0201; DPB1*0401; DQA1*0101/*0104	+

[a]Figure 3; Tables 3 & 4: references available upon request
[b]Figure 3; Tables 3 & 4: increased risk with lower 95% CI of =1.0 in one (+) or more (++) studies
[b]Figure 3; Tables 3 & 4: decreased risk with upper 95% CI of =1.0 in one (-) or more (--) studies

Risk Assessment Implications

- The multi-stage model for childhood ALL identifies the three periods--preconceptional, prenatal, and postnatal--as potentially critical windows of exposure.
- It is possible that exogenous agents may be associated with one of the windows (e.g., postnatal) more strongly than others, and appropriate animal models would be necessary to elucidate this potential association.
- Together or separately, childhood ALL-associated fusion genes and genetic polymorphisms may be used as indicators of susceptibility and increase risk.
- The disease risk is influenced by the risk factors of different origins: environmental (Figure 3), others (Table 3), and genetic (Table 4). These different risk factors may interact synergistically (additive, multiplicative, or antagonistic) in determining a child's risk of ALL. Incorporating the effects of such interactions is likely to improve the health risk assessment of childhood leukemias.

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